Prophylactic anti-staphylococcal antibiotics for cystic fibrosis (Review)

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[Intervention Review]

Prophylactic anti-staphylococcal antibiotics for cystic fibrosis

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ABSTRACT

Background

Staphylococcus aureus causes pulmonary infection in young children with cystic fibrosis. Prophylactic antibiotics are prescribed hoping to prevent such infection and lung damage. Antibiotics have adverse effects and long-term use might lead to infection with *Pseudomonas aeruginosa*.

Objectives

To assess continuous oral antibiotic prophylaxis to prevent the acquisition of *Staphylococcus aureus* versus no prophylaxis in people with cystic fibrosis, we tested these hypotheses. Prophylaxis:

1. improves clinical status, lung function and survival;

2. causes adverse effects (e.g. diarrhoea, skin rash, candidiasis);

3. leads to fewer isolates of common pathogens from respiratory secretions;

4. leads to the emergence of antibiotic resistance and colonisation of the respiratory tract with *Pseudomonas aeruginosa*.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register, comprising references identified from comprehensive electronic database searches, handsearches of relevant journals and abstract books of conference proceedings. Companies manufacturing anti-staphylococcal antibiotics were contacted.

Most recent search of Register: 04 September 2014.

Selection criteria

Randomised trials of continuous oral prophylactic antibiotics (given for at least one year) compared to intermittent antibiotics given 'as required', in people with cystic fibrosis of any disease severity.

Data collection and analysis

The authors assessed studies for eligibility and methodological quality and extracted data.

Main results

We included four studies, totaling 401 randomised participants aged zero to seven years on enrolment. The two older studies generally had a higher risk of bias across all domains, but in particular due to a lack of blinding and incomplete outcome data, than the two more recent studies. We only regarded the most recent study as being generally free of bias, although even here we were not certain of the effect of the per protocol analysis on the study results.

Fewer children receiving anti-staphylococcal antibiotic prophylaxis had one or more isolates of *Staphylococcus aureus*. There was no significant difference between groups in infant or conventional lung function. We found no significant effect on nutrition, hospital admissions, additional courses of antibiotics or adverse effects. There was no significant difference in the number of isolates of *Pseudomonas aeruginosa* between groups, though there was a trend towards a lower cumulative isolation rate of *Pseudomonas aeruginosa* in the prophylaxis group at two and three years and towards a higher rate from four to six years. As the studies reviewed lasted six years or less, conclusions cannot be drawn about the long-term effects of prophylaxis.

Authors' conclusions

Anti-staphylococcal antibiotic prophylaxis leads to fewer children having isolates of *Staphylococcus aureus*, when commenced early in infancy and continued up to six years of age. The clinical importance of this finding is uncertain. Further research may establish whether the trend towards more children with CF with *Pseudomonas aeruginosa*, after four to six years of prophylaxis, is a chance finding and whether choice of antibiotic or duration of treatment might influence this.

PLAIN LANGUAGE SUMMARY

Giving antibiotics regularly to people with cystic fibrosis to prevent infection with a germ called *Staphylococcus aureus*

Review question

We reviewed the evidence about the benefits and adverse effects of giving regular antibiotics to people with cystic fibrosis to prevent infection with a germ called *Staphylococcus aureus*.

Background

Cystic fibrosis blocks the airways with mucus and causes frequent airway infections. These can lead to death from breathing failure. People with cystic fibrosis are sometimes given regular antibiotics to prevent infections from a germ called *Staphylococcus aureus*. However, antibiotics can also have adverse effects.

Search date

The evidence is current to: 04 September 2014.

Study characteristics

The review includes four studies with 401 children; there were no adult studies. Volunteers were put into groups at random and received either an oral antibiotic continuously as a prevention for at least one year or no antibiotic treatment to prevent infection with *Staphylococcus aureus*. All volunteers could be given additional antibiotics if their doctor thought they needed them based on symptoms and germs grown in their respiratory secretions. Studies lasted for a maximum of six years.

Key results

The review found some evidence that giving regular antibiotics to young children (continued up to six years of age) leads to less infection with *Staphylococcus aureus*. For other outcomes in the review, there was no difference between giving regular antibiotics or not. Since none of the studies lasted longer than six years, we can't draw any conclusions about long-term use. Also, since all studies were in children, we can not comment on the use of these drugs in adults. Future research should look at patterns of antibiotic resistance and patient survival.

Quality of the evidence

All the studies were of variable quality. We judged that the two older studies had a higher risk of bias overall compared to the two newer studies. In particular this was because those taking part in the studies (or their parents or caregivers) would be able to guess which treatment they were receiving, and also one study did not state if anyone had dropped out and if so what the reasons were. Only the

newest study seemed to be free of bias, although even here we were not certain if the study results were affected by the way the data were analysed.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is a genetic disorder characterised by viscid secretions, primarily affecting the respiratory tract and the gut. Poor clearance of respiratory secretions and an increased susceptibility to respiratory infection lead to chronic inflammation and ultimately to bronchiectasis. Most deaths from CF are due to end-stage respiratory failure (Kerem 1992).

Bacterial infection due to *Staphylococcus aureus* (*S. aureus*) may be found in CF infants as early as three months of age (Armstrong 1995). Infection in infants with CF is accompanied by evidence of inflammation and is implicated in the development of lung damage in CF. Many older people with CF acquire chronic infection with strains of *Pseudomonas aeruginosa* (*P. aeruginosa*) and acquisition of this organism is associated with an increase in symptoms and a decline in lung function (Kerem 1990).

Description of the intervention

Most CF centres treat people with CF with antibiotics when they are symptomatic, guided by the results of recent specimens of respiratory secretions. Many will also collect sputum and 'cough swab' specimens routinely and prescribe antibiotics if a potential pathogen is found, even if the person is asymptomatic. People with CF with advanced lung disease may spend prolonged periods in hospital receiving courses of intravenous antibiotics.

It is the practice, in some CF centres, to give continuous antibiotic prophylaxis to people with CF from diagnosis. An antibiotic which is active against *S. aureus* (such as flucloxacillin) is usually chosen.

How the intervention might work

The aim of prophylactic antibiotic use in this population is to reduce infection and inflammation in the developing lung and to slow the onset of bronchiectasis. However, prophylactic antibiotics may be inconvenient to administer and may be associated with adverse effects such as diarrhoea or oral candidiasis.

Why it is important to do this review

Of greater concern is the possibility that the use of continuous antibiotic prophylaxis may lead to colonisation of the respiratory tract with strains of *S. aureus* which are resistant to many antibiotics (multiple resistant *S. aureus* or methicillin-resistant *S. aureus* (MRSA)). Furthermore, it has been suggested that the use of antibiotic prophylaxis might predispose to the acquisition of chronic infection with *P. aeruginosa* (Nolan 1982). Finally, the cost of treatment is appreciable - for an infant one year's treatment with flucloxacillin costs more than £200 (US$325) (BNF 2004).

OBJECTIVES

To assess the effect of continuous oral antibiotic prophylaxis compared to no prophylaxis to prevent the acquisition of *Staphylococcus aureus* on the outcome in people with CF. The following hypotheses were tested to investigate whether antibiotic prophylaxis:

1. improves clinical status;
2. improves lung function;
3. improves survival;
4. causes adverse effects (diarrhoea, skin rash, candidiasis);
5. leads to fewer isolates of common pathogens from respiratory secretions;
6. leads the emergence of antibiotic resistance and to the colonisation of the respiratory tract with organisms such as *P. aeruginosa*.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs). Cross-over studies were not considered because we felt this study design would not allow evaluation of the effects of prophylaxis on long-term outcome measures

such as lung function, nutrition and the acquisition of resistant organisms.

Types of participants

People with CF, of any age, diagnosed on the basis of clinical criteria and sweat testing or genotype analysis.

Types of interventions

Any oral prophylactic antibiotic, used continuously for a period of at least one year, compared with controls who do not receive prophylactic antibiotics to prevent the acquisition of *Staphylococcus aureus*. Both groups could receive intermittent courses of antibiotics 'as required', on the basis of symptoms and organisms found in respiratory secretions.

Types of outcome measures

Primary outcomes

1. Lung function - forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)
2. Number of people with one or more isolates of *S. aureus* (sensitive strains)

NB: in only one study were the children old enough to perform the lung function tests. We also included a study measuring infant lung function.

Secondary outcomes

1. Growth as measured by weight for age and height for age standard deviation scores*
2. Survival on a yearly basis commencing at one year
3. Number of people admitted to hospital and days spent as an inpatient
4. Number of people receiving additional antibiotics and number of days received
5. Number of people with one or more isolates of *Haemophilus influenzae* (*H. influenzae*)
6. Number of people with one or more isolates of *P. aeruginosa*
7. Acquisition of multiply resistant *S. aureus*
8. Frequency of adverse effects including: diarrhoea; skin rash; and oral, nappy or vulval candidiasis
9. Quality of life (if well validated measures are used)

* standard deviation score = observed weight or height - mean/ standard deviation

Search methods for identification of studies

Electronic searches

We identified relevant trials from the Group's Cystic Fibrosis Trials Register using the terms: antibiotics AND (staphylococcus aureus OR mixed infections) AND (preventative treatment OR unknown) AND (oral OR not stated).

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), quarterly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cystic Fibrosis and Genetic Disorders Group Module.

Date of the most recent search of the Group's CF Trials Register: 04 September 2014.

Searching other resources

We have checked the reference lists of the trials on the Cochrane CF and Genetic Disorders Group relevant to this review to find any studies not previously identified.

We have contacted the authors of published trials to obtain any unpublished observations or long-term follow-up data. We also wrote to the manufacturers of antibiotics commonly used as prophylaxis to establish if unpublished data are held on file. Ten manufacturers were approached: Smith Kline Beecham; Ashbourne Pharmaceuticals; Approved Prescription Services; Galen; Trinity Pharmaceuticals; Yamanouchi Pharma; Bristol Myers Squibb Pharmaceuticals; Glaxo Wellcome; Eli Lilley; and Kent Pharmaceuticals. Five of these replied, but no new data were uncovered.

Data collection and analysis

Selection of studies

Two authors independently selected studies for inclusion in the review. The authors resolved disagreements as to which studies should be included by negotiation.

Data extraction and management

Each author recorded the following: concealment of treatment allocation; generation of allocation sequence; blinding; and whether intention-to-treat analysis had been used or was possible from the

available data. Each author extracted data independently. The authors collected data for the outcome events listed above.
Where possible, the authors reported all outcome measures at yearly intervals or calculated annualised rates.

Assessment of risk of bias in included studies

In order to assess the risk of bias for each study, two authors independently assessed their methodological quality according to the method described by Schulz (Schulz 1995).
In the current version of the review, the authors assessed the risk of bias to each included study relative to six domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other potential sources of bias) as recommended by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). If the generation of allocation sequence or concealment of that sequence was deemed to be adequate, then the authors judged the study to have a low risk of bias. If these were deemed to be inadequate, then the authors judged the study to have a potential risk of bias. If these were unclear, then the risk of bias for the study was also unclear. For blinding, the risk of bias was judged to increase as the number of people blinded to the intervention decreased. The authors also deemed there to be a risk of bias if there were any withdrawals or drop outs from the study which were not accounted for and explained, or if there were an unequal number of drop outs from a particular intervention group. The authors planned to examine the protocol for each included trial where possible to establish whether results from any outcomes measured were selectively reported. Where protocols were not available, the authors compared the 'Methods' sections of the published papers to the 'Results' sections and also used clinical experience to judge whether they would expect outcomes to be measured as 'standard'. If they identified any outcomes that had been clearly measured but not reported, they judged there to be a high risk of bias; if all outcomes measured were clearly reported, they judged there to be a low risk of bias; if it was not clear if outcomes may have been measured and not reported, they judged there to be an unclear risk of bias. Finally, the authors assessed the studies for any other potential sources of bias, again judging there to be a high risk of bias if any sources were identified, a low risk of bias if it was clear that there were no other sources of bias and an unclear risk of bias if they were not able to judge this without any doubts.

Measures of treatment effect

The authors calculated a pooled estimate of treatment effect across all studies: the odds ratio for dichotomous variables and mean difference for continuous variables. For longitudinal data, the authors undertook analysis at six months and thereafter at yearly intervals from diagnosis.

Unit of analysis issues

The authors did not consider cross-over studies because they felt this study design would not allow evaluation of the effects of prophylaxis on long-term outcome measures such as lung function, nutrition and the acquisition of resistant organisms.

Dealing with missing data

Where insufficient data were available from published work, the authors requested additional data from the trial investigators.

Assessment of heterogeneity

The authors tested for heterogeneity between study results using the Chi^2 test.

Assessment of reporting biases

In future updates of this review, if the authors are able to include sufficient studies (at least 10), they plan to assess publication bias by constructing a funnel plot. If the funnel plot is not symmetrical, publication bias may be present. However, there are other reasons for funnel plot asymmetry (i.e. heterogeneity), so the authors will interpret any results with caution. To minimise publication bias, the authors plan to search trial registries for any unpublished trials and contact experts in the field.

Data synthesis

The authors analysed the data in the review using a fixed-effect model. If in future, the authors identify a moderate to high degree of heterogeneity, they will analyse the data using a random-effects model.

Subgroup analysis and investigation of heterogeneity

The authors did not plan or undertake any subgroup analyses.

RESULTS

Description of studies

Results of the search

Of a total of 18 studies identified by the searches, four studies were included and 14 studies were excluded .

Included studies

Four studies met the inclusion criteria (Chatfield 1991; Schlesinger 1984; Stutman 2002; Weaver 1994). These studies enrolled a total of 401 children and provided data from a total of 305 children (144 boys) who completed treatment per protocol (randomised to receive either prophylactic antibiotics or no prophylaxis). The most recently published study is by Stutman and colleagues, who have supplied data to us directly (Stutman 2002).

A second study (Chatfield 1991) has been the subject of three abstracts (Owen 1991; West 1990; Williams 1988), where only summary statistics have been presented, and one full paper by Chatfield, which made reference to the methodology, but which did not present results by antibiotic groups (Chatfield 1991). Individual patient data have been obtained from the authors and this study was included in the previous version of this review. Of the remaining studies, one has been published in abstract form (Schlesinger 1984) and the other has been the subject of two publications by Beardsmore and Weaver (Beardsmore 1994; Weaver 1994).

In the Chatfield study, a neonatal screening programme operated on alternate weeks and so infants were identified both clinically and by screening. Randomisation, either to continuous prophylactic flucloxacillin or 'as required' antibiotic treatment, took place at diagnosis. Many clinicians declined to randomise infants presenting with meconium ileus, and these infants were therefore excluded from the analysis (27 infants). In total, 122 infants were randomised. There were two withdrawals: one child (on prophylactic antibiotics) died at 17 weeks; another child (intermittent antibiotics) was lost to follow up. No other data were available on the infants withdrawn. Of the 120 participants who received treatment per protocol, 54 were randomised to prophylaxis and 66 to 'as required' treatment.

Schlesinger used a cycle of antibiotics (cotrimoxazole, cefadroxil and dicloxacillin), with changes being made every three months, versus the same drugs being used intermittently (Schlesinger 1984). The observation period was one year. Children aged one to seven years with mild pulmonary disease were studied. Twenty-eight children were randomised (14 to prophylaxis and 14 to control). No withdrawals were reported.

In the study by Weaver a single prophylactic antibiotic was used continuously for two years (flucloxacillin 125 mg twice daily) (Weaver 1994). In total, 42 infants were randomised and four were withdrawn (no data available). Of the 38 who received treatment per protocol, 18 received prophylaxis and 20 'as required' treatment.

Stutman and colleagues studied 209 children, from 27 CF centres in North America, enrolled before two years of age (Stutman 2002). They were diagnosed clinically and randomised to receive prophylaxis with cephalexin or to receive placebo. The withdrawal rate was high (90 children withdrawn; 119 completed the study, of which 68 were in the prophylaxis group and 51 in the placebo group). When children were withdrawn, this was most commonly at the parents' request, due to "the rigors of the study". Follow up was for six years.

In each of these studies additional antibiotics could be prescribed to children in both arms of the study. In the Stutman study, children who received an additional antibiotic stopped their prophylaxis temporarily and, if additional treatment was required for more than six weeks, the participant was withdrawn (Stutman 2002). The use of additional antibiotics in all four studies is a potential confounding factor.

Excluded studies

A total of 14 studies were excluded from the review. Cross-over studies were not considered (*see* 'Types of studies'). This resulted in the exclusion of one study (Loening-Baucke 1979). A study comparing two prophylactic antibiotics and which did not include a placebo group was also excluded (Harrison 1985). For similar reasons, we excluded two studies looking at a group of participants receiving oral prophylaxis where an additional antibiotic was given by aerosol (Nolan 1982) or parenterally (Shapera 1981). One study was a pharmacokinetic study of linezolid (Keel 2011) and another study was of a new formulation of tobramycin (Keller 2010). Finally, non-randomised studies were excluded (Ballestero 1992; Brown 1980; Denning 1977; Feigelson 1993; Jensen 1990; Kerrebijn 1984; Szaff 1982; Wright 1970).

Risk of bias in included studies

In order to establish a risk of bias, the methodological quality of each study was assessed using the criteria described by Schulz as adequate, inadequate or unclear (*see* table 'Characteristics of included studies') relating to a low, high or unclear risk of bias (Schulz 1995). Briefly, these criteria evaluate concealment of treatment allocation schedule, generation of allocation sequence, blinding and whether analysis is by intention-to-treat.

Allocation

Two studies described the method of generating the allocation sequence and was judged to have a low risk of bias (Stutman 2002; Weaver 1994). The Stutman study randomised participants in blocks of six, stratified by initial respiratory culture status (Stutman 2002). The Weaver study employed block randomisation (Weaver 1994). Two studies were described as 'randomised' but do not discuss the generation of allocation sequence in their publications; hence these were judged to have an unclear risk of bias (Chatfield 1991; Schlesinger 1984).

The two studies which described the method of randomisation, also discussed allocation concealment and the methods were judged to be adequate leading to a low risk of bias (Stutman 2002; Weaver 1994). In the Stutman study, all investigators apart from the study pharmacist were blind to treatment allocation. The pharmacist was responsible for increasing the dose of the prophylactic

antibiotic as the children grew (Stutman 2002). In the Weaver study allocation was given by telephone from the co-ordinating centre and concealed from the local investigator until the participant was enrolled (Weaver 1994). The remaining two studies did not discuss concealment of allocation and were judged to have an unclear risk of bias (Chatfield 1991; Schlesinger 1984).

Blinding

Only one of the included studies was double-blinded and placebo controlled (Stutman 2002). The authors judged this study to have a low risk of bias.

The other three studies were not blinded and did not use a placebo (Chatfield 1991; Schlesinger 1984; Weaver 1994). These studies were judged to have a potential risk of bias.

Incomplete outcome data

One study did not report any participants withdrawn from the study (Schlesinger 1984). Two studies performed analysis on those participants who completed the study and did not provide any data on participants withdrawn from the studies (Chatfield 1991; Weaver 1994). Chatfield reported data on varying numbers of participants at one, two and three year time points (Chatfield 1991). Weaver stated that analysis was per protocol (Weaver 1994). In the Stutman study, analysis was per protocol (outcome variables measured yearly up to six years of age) (Stutman 2002). The authors also analysed data on those completing at least one year of the study, although this does not constitute a formal intention-to-treat analysis (Stutman 2002). The use of per protocol analysis in the Stutman study will tend to favour the intervention.

Selective reporting

The authors judged two studies to have a low risk of bias; one study reported outcome variables at one and two years following study entry (Weaver 1994); another study measured and reported those stated outcomes yearly up to six years of age (Stutman 2002).

The authors judged two studies to have an unclear risk of bias. One study reported outcome variables at only one year after enrolment; furthermore, the protocol was not available and since this study has only been published as a abstract, the authors were unable to compare any detailed methods with results (Schlesinger 1984). The final study reported outcomes up to three years of age; however as stated above, only summary statistics have been presented in the three abstracts published for this study and the only full paper describes the methodology but does not present results by antibiotic groups (Chatfield 1991).

Other potential sources of bias

For one study there is a high risk of bias as the original data were published only in abstract form and the authors cannot be traced (Schlesinger 1984).

In each of these studies additional antibiotics could be prescribed to children in both arms of the study and the use of additional antibiotics is a potential confounding factor. However, the authors still judge there to be is a low risk of bias for this domain for the other three studies as they have not identified any other potential sources of bias (Chatfield 1991; Stutman 2002; Weaver 1994).

One study stated that the investigators performed a sample-size calculation when designing the trial (Stutman 2002).

Effects of interventions

Data from three studies could be combined (Chatfield 1991; Stutman 2002; Weaver 1994). In each case data on participants completing the study per protocol were used. The Stutman study is the only one giving data beyond three years and hence graphical data for years four, five and six refer to the Stutman study alone (Stutman 2002). In these three studies, additional antibiotics could be given to children receiving prophylaxis, when they were unwell, and so prophylaxis is evaluated as an adjunct to 'as required' treatment.

Primary outcomes

1. Lung function

Stutman used conventional tests of lung function, measured at the end of follow up (six years) (Stutman 2002). They found no significant difference between prophylaxis and placebo for FEV_1, mean difference (MD) 0.00 (95% confidence interval (CI) -0.08 to 0.08) or FVC, MD 0.10 (95% CI 0.01 to 0.19).

Infant lung function was measured by Beardsmore in the Weaver study, which looked at infants enrolled in the newborn period (Beardsmore 1994). The authors aimed to measure lung function shortly after diagnosis (achieved in 19 infants receiving prophylaxis and 18 on 'as required' treatment) and again at one year (achieved in 18 infants receiving prophylaxis and 17 on 'as required' treatment). Specialised tests of lung function (not in routine clinical practice) were used, namely: thoracic gas volume (TGV); airway conductance (Gaw); maximum flow at functional residual capacity (Vmax FRC). The study authors reported no significant difference in infant lung function between the two regimens at either age. The results were expressed as scores (the number of standard errors by which the participant's value differed from a predicted value). For the mean values of scores, please refer to the additional table (Table 1).

2. Number of people with one or more isolates of *S. aureus* (sensitive strains)

Reporting of the presence of organisms in the respiratory secretions is difficult to standardise, since prevalence is dependent on the frequency with which samples are taken. The eligible studies involved young children and so nose and throat swabs were used, rather than sputum samples. Armstrong showed that oropharyngeal specimens predict lower respiratory infection poorly (positive predictive value 41%) (Armstrong 1996).

The Weaver study reported the number of children in whom an organism was found and the number of months when there were positive isolates (Weaver 1994). However, the methods section does not specify how often routine samples were taken. For the sake of clarity and comparability, the data presented in 'Data and analyses' show the number of children with at least one isolate of *S. aureus*. Pooled data from the Chatfield, Stutman and Weaver studies were used and are presented by years in the study from one to six years (Chatfield 1991; Stutman 2002; Weaver 1994). These data show significantly fewer children with one or more isolates of *S. aureus* (at any time from the start of the study) in the group receiving prophylaxis for every year of follow up (*see* 'Analysis 1.2').

Schlesinger reported only the results of throat swabs at the beginning and end of the one-year prophylaxis period (Schlesinger 1984). The results are given for *S. aureus* only:

Start of study: prophylaxis = 2 out of 14; 'as required' treatment = 7 out of 14

End of study: prophylaxis = 0 out of 14; 'as required' treatment = 5 out of 14

Given the lower prevalence of *S. aureus* at the start of this study in participants who were subsequently randomised to prophylaxis, the finding that *S. aureus* was isolated from none of the participants receiving prophylaxis at the end of the study must be interpreted with caution. The results do not give cumulative isolation rates for the one-year study period and so are not included in 'Data and analyses'.

Secondary outcomes

1. Growth

Four studies measured children's growth (Chatfield 1991; Schlesinger 1984; Stutman 2002; Weaver 1994). Schlesinger reported the weight for age standard deviation score (Z score) after 12 months and found a statistically significant difference in favour of the children receiving prophylaxis; the statistical test used and the level of significance were not stated (Schlesinger 1984). The results from the Schlesinger study could not be presented graphically as the standard deviations were not given. Stutman and colleagues gave mean weight and height in each group, at the end of six years follow up (no significant difference) (Stutman 2002). However, standard deviation scores were not given.

Weaver recorded weight for age and length for age standard deviation scores at six months, one year and two years (Weaver 1994). Chatfield recorded the same standard deviation scores at one, two and three years (Chatfield 1991). The results for the one- and two-year assessment have therefore been combined. The combined data from the two studies did not find a statistically significant difference in either the weight for age or the length for age standard deviation scores, in favour of either regimen, at either the one- or two-year time points (*see* 'Analysis 1.3; Analysis 1.4'). The standard deviation scores at six months and three years, for the individual studies, are also presented in 'Data and analyses'. Again, there was no significant difference in favour of either regimen. Length is difficult to measure accurately in this age group.

2. Survival

This could not be included in the graphs as an outcome. No deaths were reported in three studies (Schlesinger 1984; Stutman 2002; Weaver 1994). One death was reported in the prophylaxis group in the other study, but no details were published (Chatfield 1991).

3. Number of people admitted to hospital and days spent as an inpatient

Frequency of hospital admissions was reported in three studies (Chatfield 1991; Stutman 2002; Weaver 1994). There was no significant difference between the two regimens in the number of participants having at least one hospital admission, odds ratio (OR) 0.96 (95% CI 0.50 to 1.86).

The mean number of days spent in hospital per child per year of the study was calculated for three studies (Chatfield 1991; Stutman 2002; Weaver 1994). There was no significant difference between the two regimens, MD 0.88 (95% CI -1.35 to 3.10).

4. Number of people receiving additional antibiotics and number of days received

Weaver described number of additional 'courses' of antibiotics given but did not define the length of a course (Weaver 1994). These data have therefore not been presented in graphical form. Additional antibiotic treatment was not reported in three studies (Chatfield 1991; Schlesinger 1984; Stutman 2002). There was no significant difference between groups for either the number of children receiving additional antibiotics, OR 0.18 (95% CI 0.01 to 3.60), or for the mean number of days received per child, MD -37.10 (95% CI -78.73 to 4.53).

5. Number of people with one or more isolates *H. influenzae*

Only one study reported isolates of *H. influenzae* (Weaver 1994). This study found no significant difference between the two reg-

imens in the number of children from whom *H. influenzae* was isolated, OR 0.64 (95% CI 0.18 to 2.31).

6. Number of people with one or more isolates of *P. aeruginosa*

This was not reported by Schlesinger (Schlesinger 1984). When the results of the Chatfield, Stutman and Weaver studies were combined, there were no significant differences between groups for this outcome (Chatfield 1991; Stutman 2002; Weaver 1994). However, the results suggest that this outcome may depend on the duration of treatment. As shown in the graph 'Analysis 1.10', after two and three years of treatment there was a trend towards fewer isolates of *P. aeruginosa* in the treatment group, but at years four, five and six the trend was towards fewer isolates of *P. aeruginosa* in the control group. However, only one study followed children up for four years or more (Stutman 2002).

Weaver reported isolates of *P. aeruginosa* in both upper respiratory and stool specimens (Weaver 1994). There was no significant difference in the isolation rate from stools in children on the two regimens.

7. Acquisition of multiply resistant *S. aureus*

None of the studies reported isolation of resistant organisms such as MRSA or *Burkholderia cepacia*.

8. Adverse effects of prophylactic antibiotics

These data were presented in one study (Stutman 2002). There was no significant difference between the groups in the occurrence of generalised rash, MD 0.40 (95% CI -0.07 to 0.87); nappy rash, MD 0.90 (95% CI -1.06 to 2.86); or increased stool frequency, MD 0.20 (95% CI -2.18 to 2.58).

9. Quality of life

Quality of life parent or child was not reported in any of the studies.

Additional outcomes which have arisen from the review

1. Clinical and radiological scoring

Although this was not an a priori hypothesis of this review, data from the Chatfield study are available for Shwachman and Chrispin-Norman scores at three years (Chatfield 1991). The Shwachman score is a clinical score which includes symptoms, clinical examination findings, nutrition and radiology (Shwachman 1958). The Chrispin-Norman score is an objective chest radiograph score (Chrispin 1974). There was no significant difference in either the Shwachman score, MD -0.23 (95% CI -2.97 to 2.51), or the Chrispin-Norman score, MD -0.27 (95% CI -1.05 to 0.51) in the 119 children in whom data were available at three years.

DISCUSSION

Cumulative data on 305 participants from the four included studies indicate that fewer children in the group receiving continuous anti-staphylococcal prophylaxis had one or more isolates of *S. aureus* (Chatfield 1991; Schlesinger 1984; Stutman 2002; Weaver 1994). However, the pooled data do not show complete eradication of *S. aureus* with the use of prophylaxis. We found no significant difference in the isolation rate of other common organisms (such as *H. influenzae* and *Streptococcus pneumoniae*) between the prophylaxis and 'as required' groups.

Although there was no significant difference between groups in the number of children having one or more isolates of *P. aeruginosa*, there was a trend towards fewer affected children in years two and three of the study and a similar trend to more children having at least one isolate of *P. aeruginosa* in years four to six. The data from the years four to six all come from one study (Stutman 2002), as none of the other studies had more than three years of follow up. These trends may be a chance finding. However, if the trend to more children having *P. aeruginosa* with a longer duration of prophylaxis is a genuine finding, then this is a cause for concern. There are two possible explanations: firstly, a period of prophylaxis of more than three years' duration predisposes to pseudomonas infection; or secondly, the use of a broad-spectrum antibiotic (cephalexin) rather than a narrow spectrum anti-staphylococcal antibiotic (flucloxacillin) predisposes to pseudomonas infection.

These possibilities should be investigated in a properly designed trial. After three years of prophylaxis, children could be randomised to stop prophylaxis or continue, and further randomised to receive either broad- or narrow-spectrum antibiotics. Many CF centres advocate lifelong prophylactic anti-staphylococcal antibiotics, which means there will be a much longer treatment period when adverse outcomes can be observed. In this respect, the risk of acquiring *P. aeruginosa* is cumulative over time and any factor which marginally increases this risk may only become evident during longer periods of follow up. The risk will also be affected by the treatment policy used in a clinic, for treating early infection with *P. aeruginosa* and by strategies used to prevent cross infection.

Data are presented for a number of clinical outcome measures: nutrition; Shwachman score; and Chrispin-Norman chest radiograph score. Nutritional data are available from three eligible studies (Chatfield 1991; Schlesinger 1984; Weaver 1994). One study suggested an improvement in weight for age standard deviation score in the prophylaxis group after one year of treatment

(Schlesinger 1984). This study could not be combined with the other two studies reporting standard deviation scores (Chatfield 1991; Weaver 1994). The pooled data from the studies of Chatfield and Weaver show no significant difference in weight for age or height for age standard deviation scores between regimens (Chatfield 1991; Weaver 1994). The Chatfield study provides data up to three years, again with no significant difference seen. This may be because this study looked at young children who are still showing rapid 'catch up' growth (Morison 1997), whereas the participants studied by Schlesinger may have already achieved this 'catch up' in weight. Alternatively, this negative result may be because there is no therapeutic effect. The data from the Chatfield study showed no significant difference in Shwachman or Chrispin-Norman scores between the two regimens (Chatfield 1991).

The requirement for additional antibiotics and hospital admission may be thought of as indirect measures of clinical status, although both these measures will be influenced by local treatment protocols and clinicians' preferences. The use of additional antibiotics is also a potential confounding factor. Admissions to hospital may also have a negative effect on the quality of life of the child and their family. The pooled data show no significant difference in additional antibiotics or hospital admissions between groups.

The reference by Beardsmore for the Weaver study suggests that antibiotic prophylaxis has no significant effect on infant lung function over a one-year period (Beardsmore 1994). This result is perhaps not surprising because a clinically important change in lung function over such a brief period would be unlikely. The measures of lung function used were of a specialised nature and are not available as a routine clinical test in most centres. Stutman found no significant difference in FEV_1 or FVC between the two groups after six years of follow up (Stutman 2002).

The eligible studies had a maximum follow-up period of six years and all the participants studied were under seven years of age. It is therefore important not to extrapolate these results to longer periods of prophylaxis or to older individuals. Only one death was reported in one of the eligible studies, and so no conclusions can be drawn about the likely effects of prophylaxis on survival. Mortality is likely to be very low in the young children studied and during such a short follow-up period.

In common with other Cochrane authors (Walters 1999), we have found it difficult to establish whether the randomisation method used in many studies allows true concealment of allocation and therefore prevents bias. It is to be hoped that medical journals will increasingly follow the recommendations of the CONSORT statement on reporting the results of randomised controlled trials (Moher 2001). One of the eligible studies included in this review by Schlesinger did not report withdrawals, making it impossible to determine whether intention-to-treat or per protocol analysis had been used (Schlesinger 1984). The two citations of the Weaver study contained discrepancies in the number of participants in prophylaxis and 'as required' groups (Weaver 1994). This suggests that data on lung function have been presented on some (but not all) of the participants who withdrew from the study. The Chatfield study has a number of methodological weaknesses (Chatfield 1991). There was a lack of proper randomisation of infants with meconium ileus, leading to their exclusion from our analysis. Neonatal screening was undertaken only on alternate weeks leading to a heterogeneous population, containing screened and unscreened infants, being randomised to prophylaxis or intermittent treatment. Data were not available on every child in the study at each time point of follow up. This has led to data on different numbers of children being reported at different time points. For an example of this, see the graphs in Statistical Analysis for weight and length standard deviation score at one, two and three years. This is a potential source of bias. The Stutman study was methodologically superior in having a clear description of concealment of allocation, allocation sequence generation, and double-blinded placebo-controlled design (Stutman 2002). However, even in this study, formal intention-to-treat analysis was not possible due to a lack of outcome data on those children who were withdrawn.

Overall the number of studies is small, and those studies which have been undertaken are of poor quality, with small numbers of participants. The effect on *S. aureus* is likely to be genuine, as it is seen in all three studies taken individually and when they are combined in the meta-analysis. It is also consistent at all time points up to six years. However, the lack of a beneficial effect of prophylaxis on any outcome measure other than *S. aureus* may be genuine or due to insufficient statistical power, bias or the 'lumping' together of different regimens. The data on *P. aeruginosa* must be interpreted with caution, as there was no statistically significant difference between regimens. Data for this outcome measure for years four to six came from the Stutman study alone, where attrition may have led to bias (Stutman 2002). The Stutman study was the only study to report on adverse effects and uncommon adverse effects may be missed in randomised trials because of the small numbers involved (Stutman 2002).

AUTHORS' CONCLUSIONS

Implications for practice

Our review includes four studies of anti-staphylococcal antibiotic prophylaxis in children with CF, with data from 305 participants. The quality of studies is concerning, with important deficiencies in each. Significantly fewer children with CF will have one or more isolates of *S. aureus* in upper respiratory secretions when anti-staphylococcal antibiotic prophylaxis is prescribed for the first six years of life. However, the importance of this finding is uncertain, as this review has not shown that this is associated with an improvement in clinical outcome measures. The currently available

evidence does not allow conclusions to be drawn regarding the effect of prophylaxis on acquisition of *P. aeruginosa*. There is no significant difference in the rate of common adverse effects.

There is insufficient evidence in this review to say whether the use of anti-staphylococcal antibiotic prophylaxis in older children or adults is beneficial or harmful. Hence, clinicians should exercise caution, if prophylactic anti-staphylococcal antibiotics are used in older individuals or for longer periods.

Implications for research

A number of studies, which were considered for this review, have been published only in abstract form or as methodological papers. Nonetheless, it is likely that important questions, such as the influence of prophylaxis on antibiotic resistance patterns and on patient survival, will remain unanswered. These issues can only be addressed by long-term follow-up studies, with careful bacteriological and clinical surveillance. It may be that a randomised intervention with antibiotic prophylaxis in children of three years and over, coupled with data collection via the evolving UK CF database (or its equivalent in other countries), might provide a suitable model for future research.

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REFERENCES

References to studies included in this review

Chatfield 1991 ***{published and unpublished data}***

* Chatfield S, Owen G, Ryley MC, Williams J, Alfaham M, Goodchild MC, et al.Neonatal screening for cystic fibrosis in Wales and the West Midlands: clinical assessment after five years of screening. *Archives of Disease in Childhood* 1991;**66**(1 Spec No):29–33.

Owen G, West J, Maguire S, Ryley H, Goodchild M, Weller PH. Continuous and intermittent antibiotic therapy in cystic fibrosis patients to age 4 years [abstract]. Proceedings of the 17th European Cystic Fibrosis Conference; 1991 June 18-21; Copenhagen, Denmark. 1991:95.

West J, Smith AW, Brown MRW, Weller PH. Longitudinal relationship between clinical status, lung infection and immune responses in young cystic fibrosis patients [abstract]. *Pediatric Pulmonology* 1990;**Suppl 5**:222.

Williams J, Alfaham M, Ryley HC, Goodchild MC, Weller PH, Dodge JA. Screening for cystic fibrosis in Wales and the West Midlands 2: Clinical evaluation [abstract]. *Excerpta Medica, Asia Pacific Congress Series* 1988;**74**:G(b)3.

Schlesinger 1984 ***{unpublished data only}***

Schlesinger E, Muller W, von der Hardt H, Schirg E, Rieger CHL. Effect of long-term continuous anti-staphylococcal antibiotic treatment in young children with cystic fibrosis [abstract]. Proceedings of the 9th International Cystic Fibrosis Congress. 1984:4.14.

Stutman 2002 ***{published and unpublished data}***

Stutman HR, Lieberman JM, Nussbaum E, Marks MI. Antibiotic prophylaxis in infants and young children with cystic fibrosis: A randomised controlled trial. *Journal of Pediatrics* 2002;**140**(3):299–305.

Stutman HR, Marks MI. Cephalexin prophylaxis in newly diagnosed infants with cystic fibrosis [abstract]. Proceedings of the 6th Annual North American Cystic Fibrosis Conference; 1992. 1992:147–8.

Weaver 1994 ***{published and unpublished data}***

Beardsmore CS, Thompson JR, Williams A, McArdle EK, Gregory GA, Weaver LT, et al.Pulmonary function in infants with cystic fibrosis: the effect of antibiotic treatment. *Archives of Disease in Childhood* 1994;**71**(2):133–7.

Weaver LT, Green MR, Nicholson K, Heeley AF, Mills J, Kuzemko JA. Continuous prophylactic flucloxacillin improves outcome of infants with cystic fibrosis (CF) detected soon after birth [abstract]. Proceedings of 63rd Annual Meeting of the British Paediatric Association; 1991; Warwick. 1991:24.

* Weaver LT, Green MR, Nicholson K, Mills J, Heeley ME, Kuzemko JA, et al.Prognosis in cystic fibrosis treated with continuous flucloxacillin from the neonatal period. *Archives of Disease in Childhood* 1994;**70**(2):84–9.

References to studies excluded from this review

Ballestero 1992 ***{published data only}***

Ballestero S, Villaverde R, Escobar H, Baquero F. Susceptibility to various anti-microbial agents of Staphylococcus aureus isolates from cystic fibrosis patients. *European Journal of Clinical Microbiology & Infectious Diseases* 1992;**11**(12):1193–4.

Brown 1980 ***{published data only}***

Brown J. Efficacy of antimicrobial drugs against staphylococci in cystic fibrosis. *Australian Paediatric Journal* 1980;**16**(3):207–9.

Denning 1977 ***{unpublished data only}***

Denning CR, Park S, Grece CA, Mellin GW. Continuous versus intermittent oral antibiotics in the management of patients with cystic fibrosis [abstract]. 18th Annual Meeting Cystic Fibrosis Club Abstracts. 1977:23.

Feigelson 1993 *{published data only}*
Feigelson J, Pecau Y. Fusidic acid in cystic fibrosis [Action therapeutique de l'acide fusidique dans la mucoviscidose]. *Pediatre* 1993;**29**(138):111–3.

Harrison 1985 *{published data only}*
Harrison CJ, Marks MI, Welch DF, Sharma BB, Baker D, Dice J. A multicentric comparison of related pharmacologic features of cephalexin and dicloxacillin given for two months to young children with cystic fibrosis. *Pediatric Pharmacology* 1985;**5**(1):7–16.

Jensen 1990 *{published data only}*
Jensen T, Lanng S, Faber M, Rosdahl VT, Hoiby N, Koch C. Clinical experiences with fusidic acid in cystic fibrosis patients. *Journal of Antimicrobial Chemotherapy* 1990;**25** (Suppl B):45–52.

Keel 2011 *{published data only}*
Keel RA, Schaeftlein A, Kloft C, Pope JS, Knauft RF, Muhlebach M, et al.Pharmacokinetics of intravenous and oral linezolid in adults with cystic fibrosis. *Antimicrobial Agents and Chemotherapy* 2011;**55**(7):3393–8. [CFGD Register: PI251]

Keller 2010 *{published data only}*
Keller M, Coates AL, Griese M, Denk O, Schierholz J, Knoch M. In-vivo data support equivalent therapeutic efficacy of a new tobramycin inhalation solution (150mg/ 1.5ml) administered by the eFlow® electronic nebuliser compared to TOBI® in the PARI LC PLUS® [abstract]. *Journal of Cystic Fibrosis* 2010;**9**(Suppl 1):S22, Abstract no: 84. [CFGD Register: PI241]

Kerrebijn 1984 *{published data only}*
Kerrebijn KF. Prospective study on the effect of daily and intermittent antibiotic treatment in cystic fibrosis. In: Lawson D editor(s). *CF: horizons*. Chichester: John Wiley and Son, 1984:273.

Loening-Baucke 1979 *{published data only}*
Loening-Baucke V, Mischler E, Myers MG. A placebo controlled trial of cephalexin therapy in the ambulatory management of patients with cystic fibrosis. *Journal of Pediatrics* 1979;**95**(4):630–7.
Loening-Baucke V, Mischler EH, Myers MG. Cephalexin compared to placebo in the management of patients with cystic fibrosis [abstract]. 19th Annual Meeting Cystic Fibrosis Club Abstracts. 1978:69.
Loening-Baucke V, Mischler EH, Myers MG. Cephalexin in cystic fibrosis: a placebo-controlled study [abstract]. *Pediatric Research* 1978;**12**(4 Pt 2):495.

Nolan 1982 *{published data only}*
Nolan G, McIvor P, Levinson H, Fleming PC, Corey M, Gold R. Antibiotic prophylaxis in cystic fibrosis: inhaled cephaloridine as an adjunct to oral cloxacillin. *Journal of Pediatrics* 1982;**101**(4):626–30.

Shapera 1981 *{published data only}*
Shapera RM, Warwick WJ, Matsen JM. Clindamycin therapy of staphylococcal pulmonary infections in patients with cystic fibrosis. *Journal of Pediatrics* 1981;**99**(4): 647–50.

Szaff 1982 *{published data only}*
Szaff M, Hoiby N. Antibiotic treatment of staphylococcus aureus infection in cystic fibrosis. *Acta Paediatrica Scandinavica* 1982;**71**(5):821–6.

Wright 1970 *{published data only}*
Wright GL, Harper J. Fusidic acid and lincomycin therapy in staphylococcal infections in cystic fibrosis. *Lancet* 1970;**1** (7636):9–14.

Additional references

Armstrong 1995
Armstrong DS, Grimwood K, Carzino R, Carlin JB, Olinsky A, Phelan PD. Lower respiratory infection and inflammation in infants with newly diagnosed cystic fibrosis. *BMJ* 1995;**310**(6994):1571–2.

Armstrong 1996
Armstrong DS, Grimwood K, Carlin JB, Carzino R, Olinsky A, Phelan PD. Bronchoalveolar lavage or oropharyngeal cultures to identify lower respiratory pathogens in infants with cystic fibrosis. *Pediatric Pulmonology* 1996;**21**(5): 267–75.

Beardsmore 1994
Beardsmore CS, Thompson JR, Williams A, McArdle EK, Gregory GA, Weaver LT, et al.Pulmonary function in infants with cystic fibrosis: the effect of antibiotic treatment. *Archives of Disease in Childhood* 1994;**71**(2):133–7.

BNF 2004
British National Formulary. http://www.bnf.org 2004.

Chrispin 1974
Chrispin AR, Norman AP. The systematic evaluation of the chest radiograph in cystic fibrosis. *Pediatric Radiology* 1974; **2**:101–5.

Higgins 2011
Higggins JPT, Altman DG, on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook of Systematic Reviews of Interventions. Version 5.1 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Kerem 1990
Kerem E, Corey M, Gold R, Levison H. Pulmonary function and clinical course in patients with cystic fibrosis after pulmonary colonisation with Pseudomonas aeruginosa. *Journal of Pediatrics* 1990;**116**(5):714–9.

Kerem 1992
Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. *New England Journal of Medicine* 1992;**326**(18):1187–91.

Moher 2001
Moher D, Schulz KF, Altman DG, for the CONSORT Group. The CONSORT statement: revised

recommendations for improving the quality of reports of parallel group randomised trials. *Lancet* 2001;**357**(9263): 1191–4.

Morison 1997
Morison S, Dodge JA, Cole TJ, Lewis PA, Coles EC, Geddes D, et al.Height and weight in cystic fibrosis: a cross sectional survey. *Archives of Disease in Childhood* 1997;**77** (6):497–500.

Owen 1991
Owen G, West J, Maguire S, Ryley H, Goodchild M, Weller PH. Continuous and intermittent antibiotic therapy in cystic fibrosis patients to age four years [abstract]. Proceedings of the17th European Cystic Fibrosis Conference; 1991 June 18-21; Copenhagen, Denmark. 1991:95.

Schulz 1995
Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment in controlled trials. *JAMA* 1995;**273**(5):408–12.

Shwachman 1958
Shwachman H, Kulczycki LL. Long term study of one hundred five patients with cystic fibrosis. *American Journal of Diseases of Children* 1958;**96**:6–15.

Walters 1999
Walters E, Walters JAE. Many reports of RCTs give insufficient data for Cochrane reviewers. *BMJ* 1999;**319** (7204):257.

West 1990
West J, Smith AW, Brown MRW, Weller PH. Longitudinal relationship between clinical status, lung infection and immune responses in young cystic fibrosis patients [abstract]. *Pediatric Pulmonology* 1990;**Suppl 5**:222.

Williams 1988
Williams J, Alfaham M, Ryley HC, Goodchild MC, Weller PH, Dodge JA. Screening for cystic fibrosis in Wales and the West Midlands 2: Clinical evaluation [abstract]. *Excerpta Medica, Asia Pacific Congress Series* 1988;**74**:G(b)3.

References to other published versions of this review

Smyth 2003
Smyth AR, Walters S. Prophylactic anti-staphylococcal antibiotics for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2003, Issue 3. [DOI: 10.1002/14651858.CD001912]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chatfield 1991

Methods	Randomised controlled trial.
Participants	Infants with CF diagnosed by neonatal screening or clinically (alternate weeks). Total enrolled = 122 (2 withdrew, n = 120, prophylaxis = 54, 'as required' = 66). Mean age at enrolment 18 weeks for prophylaxis & 22 weeks for 'as required'. Followed up to age three years. Data available at one, two & three years
Interventions	Continuous oral flucloxacillin versus intermittent antibiotics 'as required'
Outcomes	*Secondary outcome 1. Growth. Secondary outcome 3. Inpatient days. Secondary outcome 5. Participants with isolates of common pathogens. Secondary outcome 6. *P. aeruginosa*.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described, unclear.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded. No placebo.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analysis: not possible (infants with meconium ileus not randomised and therefore excluded from analysis). One participant lost to follow up and one infant died
Selective reporting (reporting bias)	Unclear risk	Study reported outcomes up to three years of age. Only summary statistics have been presented in abstracts, and full paper describes the methodology, but does not present results by antibiotic groups
Other bias	Low risk	No other potential source of bias identified.

Schlesinger 1984

Methods	Randomised controlled trial.
Participants	Children aged 1 to 7 years with mild CF lung disease. 28 participants enrolled, no withdrawals documented (prophylaxis = 14, 'as required' = 14). Mean age at enrolment 42 months for prophylaxis & 53 months for 'as required'. Similar Z-scores for weight & height on enrolment. Important differences in prevalence of S. aureus in prophylaxis (2/14) & 'as required' groups (7/14) on enrolment. Follow up for 1 year. Data collected at enrolment & 1 year.
Interventions	Co-trimoxazole, or cefadroxil, or dicloxacillin in 3-monthly cycles for 1 year
Outcomes	Secondary outcome 1. Growth. Secondary outcome 5. Participants with isolates of common pathogens
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described, unclear.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded. No placebo.
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat analysis: not possible, (numbers assessed for eligibility and participants withdrawn not described)
Selective reporting (reporting bias)	Unclear risk	Study reported outcome variables at only one year after enrolment. Published as abstract only, so not able to compare Methods and Results sections
Other bias	High risk	The original data were published only in abstract form and the authors cannot be traced

Stutman 2002

Methods	Randomised controlled trial.
Participants	Children under 2 years. 209 enrolled, 90 withdrew & 119 completed the study (68 prophylaxis, 51 'as required') . Mean age at enrolment (prophylaxis = 14.1 months, 'as required' = 12.7 months). Followed up for between 5 & 7 years. Data collected at yearly intervals from year 1
Interventions	Continuous cephalexin versus placebo.
Outcomes	Primary outcome 1. Lung function. Secondary outcome 1. Growth. Secondary outcome 3. Inpatient days. Secondary outcome 4. Courses of 'as required' oral antibiotics. Secondary outcome 5. Participants with isolates of common pathogens. Secondary outcome 6. *P. aeruginosa*.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participant stratified by respiratory culture status. Permuted block design (blocks of 6, with 3 participants in each block randomised to cephalexin or placebo)
Allocation concealment (selection bias)	Low risk	Treatment allocation known only to the study pharmacist. The pharmacist was responsible for increasing the dose of the prophylactic antibiotic as the children grew
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded & placebo-controlled.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Formal intention-to-treat analysis: not possible. However, analysis performed of children completing treatment per protocol (n = 119) and those completing at least 1 year of the trial (n = 165)
Selective reporting (reporting bias)	Low risk	Measured and reported stated outcome variables yearly up to six years of age
Other bias	Low risk	No other potential source of bias identified.

Weaver 1994

Methods	Randomised (block randomisation) controlled trial. Allocation was given by telephone from the co-ordinating centre and concealed from the local investigator until the participant was enrolled
Participants	Infants with CF diagnosed by neonatal screening. 42 participants enrolled, 4 withdrew (n = 38 prophylaxis = 18, 'as required' = 20). Similar mean ages at enrolment (7 weeks for prophylaxis, 5 weeks for 'as required'). Followed up to age 2 years. Data collected at 6 months, 1 & 2 years
Interventions	Continuous oral flucloxacillin versus intermittent antibiotics 'as required'
Outcomes	Primary outcome 1. Lung function. Secondary outcome 1. Growth. Secondary outcome 2. Inpatient days. Secondary outcome 4. Courses of 'as required' oral antibiotics. Secondary outcome 5. Participants with isolates of common pathogens Secondary outcome 6. *P. aeruginosa*. Secondary outcome 7. MRSA.
Notes	Additional information from authors.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Described as randomised in the published paper. Authors confirmed treatment was allocated on the basis of block randomisation and allocation was given by telephone from the co-ordinating centre
Allocation concealment (selection bias)	Low risk	Allocation of treatment was concealed from the local investigator until the participant was enrolled
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded. No placebo.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analysis: not possible.
Selective reporting (reporting bias)	Low risk	Study reported outcome variables at one and two years following study entry
Other bias	Low risk	No other potential source of bias identified.

*Numbering of outcomes relates to order of outcomes in text of review.

CF: cystic fibrosis
MRSA: methicillin-resistant *Staphylococcus aureus*
P. aeruginosa: *Pseudomonas aeruginosa*
S. aureus: *Staphylococcus aureus*

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ballestero 1992	Non-randomised.
Brown 1980	Non-randomised.
Denning 1977	Non-randomised.
Feigelson 1993	Non-randomised.
Harrison 1985	Both participant groups received prophylaxis. Comparison was not made with a group receiving intermittent antibiotics 'as required'
Jensen 1990	Non-randomised.
Keel 2011	Pharmacokinetic study of linezolid.
Keller 2010	Study of new formulation of tobramycin for use in treating *Pseudomonas aeruginosa*.
Kerrebijn 1984	Non-randomised.
Loening-Baucke 1979	Cross-over study design.
Nolan 1982	All participants on oral prophylaxis (cloxacillin). Nebulised cephaloridine given to alternate participants in a quasi-randomised design
Shapera 1981	Parenteral and oral clindamycin versus oral clindamycin alone
Szaff 1982	Non-randomised.
Wright 1970	Non-randomised.

DATA AND ANALYSES

Comparison 1. Continuous, oral, anti-staphylococcal antibiotic prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lung function	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 FEV_1 at 6 years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 FVC at 6 years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Number of children from whom *S. aureus* isolated at least once	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 1 year	2	248	Odds Ratio (M-H, Fixed, 95% CI)	0.27 [0.15, 0.48]
2.2 2 years	3	315	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.13, 0.35]
2.3 3 years	2	260	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.13, 0.38]
2.4 4 years	1	127	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.04, 0.25]
2.5 5 years	1	98	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.03, 0.26]
2.6 6 years	1	43	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.03, 0.46]
3 Z score weight (6 months to 3 years)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 6 months	1	32	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.54, 1.14]
3.2 1 year	2	133	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.50, 0.26]
3.3 2 years	2	140	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.33, 0.45]
3.4 3 years	1	112	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.58, 0.30]
4 Z score length (6 months to 3 years)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 6 months	1	23	Mean Difference (IV, Fixed, 95% CI)	0.52 [-0.36, 1.40]
4.2 1 year	2	127	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.36, 0.48]
4.3 2 years	2	134	Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.65, 0.19]
4.4 3 years	1	112	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.50, 0.36]
5 Number of children requiring admission (annualised rates)	3	243	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.50, 1.86]
6 Days in hospital (annualised rates)	3	242	Mean Difference (IV, Fixed, 95% CI)	0.88 [-1.35, 3.10]
7 Number of children receiving additional antibiotics	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Days of additional antibiotics	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Number of children from whom *H. influenzae* isolated at least once	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 2 years	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Number of children from whom *P. aeruginosa* isolated at least once	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 1 year	2	247	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.77, 2.60]
10.2 2 years	3	315	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.45, 1.23]
10.3 3 years	2	261	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.51, 1.51]
10.4 4 years	1	127	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [0.62, 2.64]
10.5 5 years	1	98	Odds Ratio (M-H, Fixed, 95% CI)	1.97 [0.85, 4.58]
10.6 6 years	1	43	Odds Ratio (M-H, Fixed, 95% CI)	3.67 [0.77, 17.35]

11 Adverse effects	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1 Generalised rash	1	119	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.07, 0.87]
11.2 Nappy rash	1	119	Mean Difference (IV, Fixed, 95% CI)	0.90 [-1.06, 2.86]
11.3 Increased stool frequency	1	119	Mean Difference (IV, Fixed, 95% CI)	0.20 [-2.18, 2.58]
12 Shwachman score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 3 years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Chrispin-Norman Score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 3 years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

ADDITIONAL TABLES

Table 1. Results of infant lung function testing (Beardsmore 1994)

Measurement	Prophylaxis (start)	As required (start)	Prophylaxis (1 year)	As required (1 year)
TGV (thoracic gas volume)	0.05	0.98	-0.22	0.09
Gaw (airway conductance)	1.16	0.00	-1.79	-1.13
Vmax FRC (maximum flow at functional residual capacity)	-0.69	-0.75	-0.61	-0.85
(All lung function values expressed as standard error scores)				

WHAT'S NEW

Last assessed as up-to-date: 20 November 2014.

Date	Event	Description
20 November 2014	New search has been performed	An updated search of the Cystic Fibrosis & Genetic Disorders Review Group's Cystic Fibsrosis Trials Register did not identify any new references which were potentially eligible for inclusion in this review The Plain Language Summary has been updated in line with new guidance
20 November 2014	New citation required but conclusions have not changed	No new information has been added to this review, therefore our conclusions remain the same

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 1, 2000

Date	Event	Description
30 October 2012	New citation required but conclusions have not changed	No new data were included at this update and so the conclusions of the review remain the same
30 October 2012	New search has been performed	A new search of the Group's Cystic Fibrosis Trials Register identified two new references potentially eligible for inclusion in this review both of which were excluded (Keel 2011; Keller 2010).
13 September 2010	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified no studies which were potentially relevant for inclusion in the review
12 August 2009	Amended	Contact details updated.
9 September 2008	Amended	Converted to new review format.
2 September 2008	New search has been performed	A new search of the Group's trials register was run but no new references were identified
23 May 2007	New search has been performed	A new search of the Group's trials register was run but no new references were identified
24 May 2006	New search has been performed	A new search of the Group's trials register was run but no new references were identified
23 February 2005	Amended	To more accurately reflect the content and scope of the review, the title was changed from 'Prophylactic antibiotics for cystic fibrosis'
23 February 2005	New search has been performed	A new search was run but no new references were identified.
29 April 2004	New search has been performed	A new search was run but no new references were identified.
20 May 2003	New citation required and conclusions have changed	Substantive amendment. Since the previous version of this review, the results of a large North American trial of cephalexin versus placebo have been published (Stutman 2002). The authors have made further data available, allowing us to evaluate the effect of prophylaxis on conventional lung function tests, number of people receiving additional antibiotics, days of additional treatment and adverse

(*Continued*)

		effects. This further data also allows pooling of data on the following outcome measures: number of people admitted to hospital, duration of admission, isolates *S. aureus*, and isolates of *P. aeruginosa*. Our earlier findings of a beneficial effect on the number of children with one or more isolates of *S. aureus*, are confirmed. There is no significant difference in the number of isolates of *P. aeruginosa* between groups, though there is a trend towards fewer children with one or more isolates of *P. aeruginosa* infection, with prophylaxis, in years two and three and a similar trend towards more children with *P. aeruginosa* from years four to six.
21 March 2001	New search has been performed	We have received individual patient data on 109 children at two-year follow up who were enrolled in the Wales and West Midlands neonatal screening study (reported by Chatfield 1991). The published report did not include analysis by allocation to the prophylaxis or intermittent treatment group. We have now gone back to the original data and undertaken this analysis. This has allowed pooling of data on the following outcome measures: nutrition, isolates of common pathogens, isolates of *P. aeruginosa,* number of children admitted to hospital, and duration of admission. Our earlier findings of a beneficial effect of prophylaxis on the frequency of isolation of *S. aureus* from upper respiratory secretions are confirmed. Pooled data demonstrate no effect on nutrition. There is a non-significant trend towards a lower prevalence of *P. aeruginosa* infection with prophylaxis.

CONTRIBUTIONS OF AUTHORS

Both AS and SW evaluated which studies should be included in the review. AS analysed the data. AS and SW both interpreted the results. AS liaised with the authors of the studies included in this review to obtain additional data.

AS completed the updates with additional comments from SW and he acts as guarantor for this review.

DECLARATIONS OF INTEREST

ARS declares relevant activities of membership of a MPEX steering committee, advisory board member (Vertex, Gilead and MPEX), lecture paid for by Gilead.

SW declares no known potential conflict of interest.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The authors included a further outcome after the protocol was published: Clinical and radiological scoring. Although this was not an a priori hypothesis of this review, data from the Chatfield study are available for Shwachman and Chrispin-Norman scores at three years (Chatfield 1991). The Shwachman score is a clinical score which includes symptoms, clinical examination findings, nutrition and radiology (Shwachman 1958). The Chrispin-Norman score is an objective chest radiograph score (Chrispin 1974).

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis; Cystic Fibrosis [*microbiology]; Infant, Newborn; Pseudomonas aeruginosa [isolation & purification]; Randomized Controlled Trials as Topic; Respiratory Tract Infections [*prevention & control]; Staphylococcal Infections [*prevention & control]; Staphylococcus aureus [*isolation & purification]

MeSH check words

Child; Child, Preschool; Humans; Infant